REMARKS

Claims 16-25 were previously cancelled. Claim 1-15 are therefore currently pending.

With entry of the current amendment, claims 1 and 15 have been amended.

The amendments to the claims add no new matter.

Claim 1 has been amended to recite detecting the formation of a specific hybrid of the amplificate and probe. Support for the amendment can be found, *e.g.*, on page 13, first full paragraph, and the last line of page 50 bridging to page 51.

Claim 15 has been amended to recite that hybridization of the probe to the amplificates is detected by means of mass spectroscopy. Support for the amendment can be found, *e.g.*, on page 35, at the second and third full paragraphs.

For convenience, the rejections will be addressed in the order presented in the Office Action mailed December 15, 2003.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 15 was rejected as allegedly indefinite. The Examiner contends that it is not clear whether the detection by mass spectroscopy is achieved with the probe bound to the detected amplifcate, or whether only the amplificate is detected. To the extent that the rejection applies to the amended claim, Applicant respectfully traverse.

Definiteness of claim language is not analyzed in a vacuum, but takes into account the content of the application, the teachings of the prior art, and the interpretation that would be give by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (*see, e.g.*, MPEP § 2173.02). The claimed method involve two primers and a probe that hybridizes to the amplified product. In one embodiment, hybridization of the probe to the amplificate is detected by mass spectroscopy. Methods of detecting hybridization of a probe to a target nucleic acid, in this case, the amplificate, are known (*see, e.g.*, Koester, cited by the Examiner in section 12 of the Office Action). The Examiner has not provided any evidence or reasoning as to why the detection step would not be understood by the skilled artisan.

Applicant submits that the claim language in claim 15 is fully compliant with the standard for determining definiteness. Withdrawal of the rejection is therefore requested.

Claim interpretation

The examiner interprets "non-specific primer" or "non-specific probe" as primers and probes that are used to amplify and detect several different targets simultaneously. The specification defines "not specific" in relation to a particular nucleic acid sequence at page 42, lines 13-16 ("A sequence is preferably not specific for a sequence when it could hybridize with other nuclei c acids under the conditions that are used to carry out the test"). Although a "non-specific primer" or "probe" can be used in a simultaneous amplification reaction, in the current invention, the combination of primers and probe for any give target nucleic acid retains its specificity, even in a simultaneous amplification reaction. This is explained in the specification, *e.g.*, on page 47, starting at the last paragraph through the first 8 lines of page 49.

Rejection under 35 U.S.C. § 102(b)

Claims 1-3, 5-7, 10, and 14 are rejected as allegedly anticipated by Birkenmeyer *et al.*, U.S. Patent No. 5,453,355 ("Birkenmeyer"). The Examiner describes Birkenmeyer as teaching primer pairs 5, 6, 8, and 9 that result in an amplification product of less than 100 nucleotides in which there are no nucleotides between primer sequences that do not belong to the complex between the amplified product and the probe (SEQ ID NO:8). She therefore argues that the claims are anticipated. Applicants respectively traverse.

The current invention relates to a specific and sensitive method of detecting a target nucleic acid sequence. The method relates to detecting the sequence by generating small amplificates and using a probe that hybridizes to essentially all of the sequence between the primer binding sites on the target nucleic acid. Birkenmeyer does not disclose this method.

As the Examiner knows, in order for a reference to be anticipatory, each element of the claims must be taught in the reference. As further explained below, the primer pairs and/or probe taught by Birkenmeyer: 1) do not result in an amplified product or do not amplify a product of 100 nucleotides or less; 2) result in an amplified product in which there are additional

nucleotides outside the probe binding region in the sequence and/or 3) do not provide specific detection of the target nucleic acid. Accordingly, Birkenmeyer does not anticipate the claimed invention.

Birkenmeyer primer pairs do not yield amplicons having the properties set forth in the claimed invention

At page 4, the Examiner points to primer pairs 5, 6, 8, and 9 in Birkenymer as amplifying DNA fragments of 57, 51, 50, and 44 bp. However, Birkenmeyer teaches that primer pairs 6 and 8 (and primer pair 4) each failed to produce amplified products that hybridized with the probe (*see, e.g.*, column 9, lines 35-40; and Figure 2). Further, amplification using primer pairs 1, 2, 3, 10, 11, and 12 results in amplicons longer than 100 nucleotides (*see, e.g.*, Table 1 and Figures 1 and 2). The steps set forth in the current claims therefore are not taught by Birkenmeyer.

Although the Examiner did not specifically cite primer pair 7, Applicant further notes that although this pair amplifies a product less than 100 nucleotide, the probe taught by Birkenmeyer (SEQ ID NO:8) does not meet the criteria set forth in the claims with respect to the primer pair 7 amplicon. For primer pair 7, SEQ ID NOs 6 and 2 bind to positions 902-914, and 972-951, respectively. Amplification of the region targeted by these primers results in an amplicon of 70 nucleotides with positions 915-950 falling between the primers. SEQ ID NO:8 hybridizes to nucleotides at positions 894-936 (Table 1, Figure). Thus, there is a large region that lies between the primer binding site of SEQ ID NO:2 and the probe that does not hybridize to the probe, *i.e.* the regions corresponding to positions 937-950. Thus, the probe does not meet the elements specified in step (c) of claim 1.

Birkenmeyer fails to teach a specific detection method.

Of the four primers pairs cited by the Examiner, only two were able to amplify products less than 100 nucleotides in length primer pairs 5 and 9. However, inspection of Figure 2 shows that the amplification reactions were not specific. In lane 5 (reaction performed with primer pair 5), the probe (SEQ ID NO:8) hybridizes to multiple bands. The reaction therefore is

not specific. Similarly, lane 9 (reaction performed with primer pair 9) shows a second product that is detected with the probe.

Only primer pair 1 was actually analyzed for specificity; however, this primer pair amplifies a segment greater than 100 nucleotides in length, i.e., the region from 827-972 of the target nucleic acid sequence. In addition, as with primer pair 7, there is a large region between primer binding sites that does not hybridize to the probe. Thus, although the probe in combination with primer pair 1 may exhibit specificity, it does not meet the other requirements of the claims.

As demonstrated above, Birkenmeyer fails to teach all of the elements set forth in claim 1. In view of this deficiency, the reference also fails to anticipate claims 2, 3, 5, 6, 7, 10, and 14. Accordingly, the claims are patentable over Birkenmeyer. Applicant therefore requests withdrawal of the rejection.

Rejection under 35 U.SC. § 103

Claim 8 stands rejected as allegedly unpatentable over Birkenmeyer and Livak *et al.*, U.S. Patent No. 5,538,848 ("Livak"). The Examiner contends that it would have been obvious to use a fluorescent dye and quencher to label the probe taught in the methods set forth in Birkenmeyer for the purpose of performing a real-time quanitification of nucleic acid amplification. Applicants respectfully traverse.

As the Examiner knows, in order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria. First, the prior art reference or combination of references must teach or suggest all of the claim elements. Second, the Examiner must show that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Third, the Examiner must show that there is a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. The Examiner's arguments fail to meet these criteria.

Birkenmeyer does not teach or suggest all of the elements of claim 1, as explained above. Although Livak teaches a dual-labeled probe, there is no teaching or suggestion that provides the elements missing in the disclosure of Birkenmeyer. Accordingly, even if the references could credibly be combined, the combination does not result in the claimed invention. Accordingly, the invention is patentable over the cited art.

Claim 9 was rejected as allegedly unpatentable over Birkenmeyer in view of Wittwer, U.S. Patent No. 6,245,514 ("Wittwer"). Wittwer is described as teaching detection of PCR products by resonance energy transfer between one labeled primer and one labeled probe that hybridizes between the PCR primers. The Examiner contends that it would have been obvious to use the donor-acceptor energy transfer between a primer and a probe using the detection method of Birkenmeyer to provide a superior monitor of product accumulation for quantification. Again, Birkenmeyer does not teach or suggest all of the elements of claim 1. Wittwer provides no further teaching to cure this deficiency. Thus, claim 9 is patentable over the combination of the references.

The rejection of claim 15 as allegedly obvious over Birkenmeyer and Koester also fails for the same reason: the combination of the cited art does not teach or suggest each element of the claimed invention. Accordingly, claim 15 is unobvious.

Claims 4 and 11-13 were also rejected as allegedly unpatentable over Birkenmeyer in view of Greisen *et al, in J. Clin. Microbiol.* 32: 335-351, 1994 ("Greisen"). The Examiner cites Greisen as teaching non-specific primers and non-specific probes that amplify and bind to multiple RNA species. Greisen does not provide the elements missing in the disclosure of Birkenmeyer. As with the other obviousness rejections, even if the references could credibly be combined, the combination of the cited art fails to provide all of the elements of the invention. Accordingly, the claims are unobvious.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 103.

Obviousness type double patenting

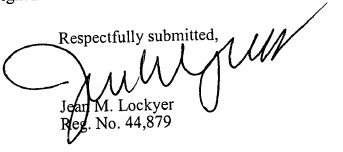
Claims 1, 4, 5, 8, and 11-14 were provisionally rejected for obviousness type double patenting over claims 1 and 3-9 of co-pending Application No. 09/530,747. Claims 1-5 were provisionally rejected for obviousness type double patenting as unpatentable over claims 1-15 of Application No. 09/530,929. According to MPEP § 822.01, "[i]f the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent…" The cited applications are not currently allowed. Accordingly, if these rejections become the only outstanding rejections, the present claims should be allowed. However, if one or both of the above-listed applications is allowed in the interim, Applicant will gladly consider providing a terminal disclaimer as necessary.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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